Telomere Biology Disorder/Dyskeratosis Congenita Panel

Clinical Features:
The telomere biology disorders (TBDs) are a set of complex diseases related to aberrant telomere biology. Genetic defects in telomeres and telomere repair appear in multiple human diseases including constitutional marrow failure as dyskeratosis congenital (DC), some apparently acquired aplastic anemia, myelodysplasia and acute myeloid leukemia; pulmonary fibrosis; and hepatic nodular regenerative hyperplasia and cirrhosis [1]. DC is a highly heterogeneous disorder characterized by abnormal skin pigmentation, nail dystrophy and oral leukoplakia (mucosal keratosis appearing as white patches in the oral cavity) [2]. This classic triad of findings is present in 80-90% of affected individuals [3]. Anticipation may be observed in affected families, and is thought to be due to the inheritance of shortened telomeres from an affected parent [3]. TBD/DC can be inherited in either an autosomal dominant, autosomal recessive or X-linked manner, depending on the causative gene. Clinically silent carriers of a TBD-associated genetic mutation have also been reported. Variable penetrance of the phenotype and/or variable expressivity of the disease-associated mutations are common [4].

Our Telomere Biology Disorder/Dyskeratosis Congenita Panels include sequence analysis and/or deletion/duplication analysis of all 10 genes listed below.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Features</th>
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<tr>
<td>C16orf57</td>
<td>Walne et al. (2010) identified homozygous mutations in the C16orf57 gene in 6 out of 132 families with dyskeratosis congenita (DC) [5]. DC has previously been associated with short telomeres, however patients with C16orf57 mutations and DC were found to have normal length telomeres [5]. Mutations in the C16orf57 gene have also been described in individuals with poikilodermatous rash (patchy skin discoloration), noncyclical neutropenia, small stature, pachyonychia, and pulmonary disease [6].</td>
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<td>CTC1</td>
<td>Keller et al. (2012) identified compound heterozygous mutations in CTC1 in a patient with DC [7]. The CTC1 gene is also associated with Coats syndrome, which is characterized by bilateral exudative retinopathy, intracranial calcifications and cysts, premature hair greying, osteoporosis and anemia [8].</td>
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<td>DKC1</td>
<td>Mutations in the X-linked DKC1 gene are the most common cause of DC [9]. Age of onset and severity of symptoms is highly variable, but affected males typically present in the first decade of life, and typically die in their twenties due to complications from bone marrow failure [9]. Many mutations occur de novo. Female heterozygous carriers are typically asymptomatic [9].</td>
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<td>NOLA3 (NOP10)</td>
<td>A homozygous mutation in NOLA3 was identified in 3 individuals with DC in a consanguineous family [10]. All three individuals had the mucocutaneous features of DC, one individual also developed bone marrow failure [10].</td>
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<td>NHP2</td>
<td>Biallelic mutations in NHP2 have been described in two patients with DC [11].</td>
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<td>RTEL1</td>
<td>Both dominant and recessive mutations in the RTEL1 gene have been associated with Hoyeraal Hreidarsson syndrome, a clinically severe variant of DC with cerebellar hypoplasia, severe immunodeficiency, enteropathy, and intrauterine growth retardation [12]. Anticipation has been described in one family where two affected males inherited a heterozygous mutation from a clinically unaffected female with short telomeres [12].</td>
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<td>TERC</td>
<td>Heterozygous mutations in the TERC gene account for approximately 4% of all cases of DC [9]. Anticipation has been observed in families with TERC-associated DC, with increased disease severity and earlier age of onset seen with successive affected generations [9].</td>
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<td>TERT</td>
<td>Heterozygous mutations in TERT have been associated with DC or aplastic anemia [9]. Penetration of these mutations appears to be reduced, with some individuals being asymptomatic [9]. Variable expressivity has also been described, with some individuals being mildly affected [9].</td>
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<td>WRAP53 (TCAB1)</td>
<td>Biallelic mutations in TCAB1 have been described in individuals with classical DC from two different families [13].</td>
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<tr>
<td>TINF2</td>
<td>Dominant mutations in TINF2 have been described in patients with DC [14]. Both inherited and de novo mutations have also been described [14, 15].</td>
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</tbody>
</table>
**Test methods:** Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

**Comprehensive Telomere Biology Disorder/Dyskeratosis Congenita panel (sequencing and deletion/duplication analysis of 10 genes)**

**Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube

**Cost:** $3900

**CPT codes:** 81407

**Turn-around time:** 6 weeks

**Note:** We cannot bill insurance for this panel.

**Telomere Biology Disorder/Dyskeratosis Congenita Sequencing Panel (sequence analysis of 10 genes)**

**Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube. NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.

**Cost:** $3200

**CPT codes:** 81407

**Turn-around time:** 6 weeks

**Note:** We cannot bill insurance for this panel.

**Telomere Biology Disorder/Dyskeratosis Congenita Deletion/Duplication Panel (deletion/duplication analysis of 10 genes)**

**Sample specifications:** 3 to 10 cc of blood in a purple top (EDTA) tube. NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.

**Cost:** $1545

**CPT codes:** 81406

**Turn-around time:** 6 weeks

**Results:**

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Telomere Biology Disorders/Dyskeratosis Congenita Sequencing Panel or Deletion/Duplication Panel. All abnormal results are reported by telephone.

**References:**


